Pragmatic and Observational Research

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SHORT REPORT

Steroidal Mineralocorticoid Receptor Antagonist Side Effects and Reasons for Discontinuation: A Patient Survey (RELICS-PS)

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Purpose: To understand steroidal mineralocorticoid receptor antagonists (sMRAs) treatment patterns and side effects from patients' perspectives.

Methods: The RELICS-PS study, a complement to the claims-based RELICS study, used a cross-sectional patient survey targeting adults with commercial or Medicare Advantage health insurance who had at least one pharmacy claim for sMRAs (spironolactone or eplerenone) between July 2021 and June 2022. It used the Healthcare Integrated Research Database (HIRD®) as the sampling frame to identify eligible patients. A total of 600 completed surveys were targeted from current and past sMRA users between November and December 2022. The survey collected data on demographics, chronic conditions, prespecified side effects, and reasons for discontinuation among past sMRA users, describing the data without inferential testing.

Results: Of 600 respondents, 49.2% reported at least one side effect. Side effects varied from 5.5% (weak pulse and chest pains) to 40.0% (sluggishness or fatigue). Reports of symptoms of male gynecomastia were noticeably higher than in medical claims in RELICS (17.4% vs 2.9%). Past users, consisting of 24.3% of respondents, were more likely to report experiencing side effects, experiencing them more frequently, and being more affected by them. Approximately a third of these respondents reported side effects as a deciding factor for discontinuation. Healthcare providers' recommendations, often informed by medication effectiveness and patient tolerance, were the most cited reason for discontinuation.

Conclusion: Although half of the respondents reported experiencing side effects, 39.0% of past users identified side effects as a reason for discontinuation. This suggests a gap between patient experience and perceived reasons for discontinuation. A notable finding from the study is the significant role of healthcare providers in influencing the decisions to start or stop sMRA treatment. Therefore, future research should focus on exploring the factors that shape healthcare providers' decision-making processes when initiating and discontinuing treatment options.

Keywords: steroidal mineralocorticoid receptor antagonists, patient reported side effects

Introduction

Steroidal mineralocorticoid receptor antagonists (sMRAs), including spironolactone and eplerenone, are utilized to manage cardiovascular (CV) and endocrine conditions.[1,2] They have demonstrated benefits in reducing the risk of CV-related hospitalizations and mortality, and in decreasing atrial fibrillation episodes.[3–6] However, the literature indicates high rates of discontinuation, potentially linked to adverse events such as hyperkalemia, deteriorating kidney function, dehydration, dizziness, nausea, and male gynecomastia.[7–12] Yet, a comprehensive understanding of patient perspectives on these side effects and reasons for discontinuation still needs to be explored.

Received: 2 August 2024
Accepted: 26 February 2025
Published: 3 April 2025

This study complements the RELICS study[10], intending to deepen understanding of real-world sMRA usage. While RELICS used a claims database to analyze treatment patterns and adverse events, reliance on such databases might underrepresent the occurrence of adverse events. To bridge this knowledge gap and complement the evidence generated from a claims-based study, this survey study aimed to elucidate sMRA treatment patterns and side effects from the patient perspective.

Methods

The RELICS-PS study was a cross-sectional patient survey targeting commercially insured or Medicare Advantage-insured adults with at least one pharmacy claim for sMRAs (spironolactone or eplerenone) between July 2021 and June 2022. This and the claims-based RELICS study used the Healthcare Integrated Research Database (HIRD®), a comprehensive healthcare database with administrative claims data for over 80 million lives. This study used the HIRD as the sampling frame to identify survey-eligible patients.

Survey respondents consisted of current or past sMRA users who responded to recruitment materials, consented to participate, met study criteria, and completed the survey. Survey fielding occurred between November 2, 2022, and December 23, 2022, when the targeted number of 600 completed surveys was obtained. Respondents were categorized as current users if they were still an sMRA user at the time of the survey or past users if they had stopped sMRA treatment in the 12 months prior to the survey date.

The survey collected demographic data and information on chronic conditions. It also inquired about six potential prespecified side effects from sMRAs, including extreme fatigue, abdominal pain, lethargy, weak pulse, confusion, and enlarged or painful breast tissue (ie, symptoms of male gynecomastia). Respondents reporting side effects were asked about the frequency and impact of these experiences on their lives. Past users were additionally asked about 13 prespecified reasons for discontinuing sMRA treatment.

Descriptive analyses were performed, reporting frequencies and percentages for categorical variables and measures of centrality and variance (ie, mean, standard deviation, median, and interquartile range) for continuous measures. No inferential statistics comparing current and past users were generated. The study presented patients' perspectives on their experiences using sMRAs. It provided an understanding of sMRA real-world usage, side effect occurrence, and reasons for discontinuation that could not be obtained from claims data.

The protocol and all survey-related materials were approved by the WCG Institutional Review Board prior to the conduct of the study and all patient data were handled in compliance with the regulations of the US Health Insurance Portability and Accountability Act of 1996. The study adhered to the ethical principles outlined in the Declaration of Helsinki, ensuring the protection of human subjects involved in the research.

Results

Overall, 2,104 of 45,000 patients responded to the recruitment material, of whom 2,010 provided electronic or verbal consent to participate, 710 met all study inclusion criteria, and 600 completed the survey (Supplementary Figure 1). Of the 600 respondents, 454 were current users (75.7%) and 146 were past users (24.3%). No major differences were detected between responders and non-responders or completers and non-completers (Supplementary Table 1).

The majority of respondents were female (75.7%), white (81.8%), spironolactone users (98.2%), and were 54 years old on average (Table 1). Past users were more likely to be female and younger than current users. Overall, 57.0% of respondents reported being diagnosed with hypertension, 28.5% with heart failure (HF), 28.0% with type 2 diabetes (T2D), 13.8% with edema in the legs or abdomen due to liver disease, and 10% with chronic kidney disease (CKD). The percentage of patients diagnosed with HF or CKD, two comorbidities used by the claims-based RELICS study to categorize new users of sMRAs, was comparable. The comorbidity burden was reportedly higher in current versus past users across all conditions.

Approximately half of all respondents reported experiencing at least one prespecified side effect (Table 2). The proportion of respondents experiencing these side effects ranged from 5.5% (weak pulse, chest pains, or signs of a heart attack) to 40.0% (feelings of fatigue or sluggishness). The number of side effects reported did not vary appreciably between current and past users. However, a higher proportion of past users reported experiencing each side effect

Table 1 Demographics and Clinical Characteristics of Respondents

N	All Respondents 600	Current Users 454	Past Users 146
Demographics			
Age, mean (SD)	54 (15.7)	56 (15.1)	48 (15.9)
Gender, %			
Male	22.5%	24.2%	17.1%
Female	75.7%	74.0%	80.8%
Non-binary/third gender	0.8%	0.9%	0.7%
I use another term	0.3%	0.4%	0.0%
Refused	0.7%	0.4%	1.4%
Race/ethnicity, %			
Hispanic	1.7%	1.3%	2.7%
White, Non-Hispanic (NH)	81.8%	81.7%	82.2%
Black or African American, NH	11.3%	12.1%	8.9%
Asian, NH	1.8%	1.3%	3.4%
Other, NH	2.6%	2.9%	1.4%
Refused	0.8%	0.7%	1.4%
Diagnosed by healthcare provider, %			
Hypertension	57.0%	60.6%	45.9%
HF	28.5%	31.1%	20.6%
Edema due to liver disease	13.8%	13.9%	13.7%
CKD	10.0%	10.8%	7.5%
T2D	28.0%	30.6%	19.9%

compared to current users, notably symptoms of male gynecomastia, which affected 33.3% of male past users but only 13.7% of male current users.

Among those reporting side effects, over 35.0% indicated they experienced the respective side effects at least once a week (Table 2). The proportion of respondents reporting frequent side effects ranged from 36.4% (weak pulse, chest pain, or symptoms of heart attack) to 65.4% (feeling tired, sluggish, or lethargic) among those experiencing these effects. Past users were affected more frequently by the side effects, especially symptoms of male gynecomastia, which was experienced frequently by 43.8% of current users and 100% of past users. Overall, respondents reported being negatively affected by side effects in their ability or willingness to engage in vigorous recreational or exercise activities (65.1%), mood or emotions (55.6%), ability to complete daily tasks (46.8%), self-esteem (43.4%), work or studies (41.7%), or relationships with family or friends (36.6%). Past users reported being more negatively affected across all domains.

Overall, 95.2% of past users reported that at least one of the 13 prespecified reasons contributed to their decision to discontinue treatment (Table 3). Fewer than 50.0% of past users reported that any individual reason contributed to their decision to discontinue treatment. However, when looked at as a composite variable, 56.2% reported that their healthcare

Table 2 Side Effects Among Respondents

	All Respondents	Current Users	Past Users
Number of side effects or related symptoms reported per respondent, %			
0	50.8%	52.0%	47.3%
1–2	35.2%	35.9%	32.9%
3–4	12.0%	10.4%	17.1%
5–6	2.0%	1.8%	2.7%
Side effects experienced[a], %			
Feeling tired, sluggish, or lethargic	40.0%	39.9%	40.4%
Extreme muscle weakness or fatigue	23.5%	22.7%	26.0%
Enlarged or sore breast tissue that may be painful or swollen (men only)	17.4%	13.7%	33.3%
Severe abdominal pain, nausea, vomiting, or diarrhea	13.0%	11.9%	16.4%
Confusion or trouble concentrating	12.7%	11.0%	17.8%
Weak pulse, chest pain, or signs of heart attack	5.5%	5.3%	6.2%
Frequently occurring side effects[b], %			
Feeling tired, sluggish, or lethargic	65.4%	62.4%	74.6%
Enlarged or sore breast tissue that may be painful or swollen (men only)	64.0%	43.8%	100%
Extreme muscle weakness or fatigue	63.8%	61.2%	71.0%
Confusion or trouble concentrating	57.9%	52.0%	69.2%
Severe abdominal pain, nausea, vomiting, or diarrhea	43.6%	44.4%	41.7%
Weak pulse, chest pain, or signs of heart attack	36.4%	29.2%	55.6%
Negatively impacted by side effects[c], %			
Ability or desire to participate in vigorous recreational or exercise activities	65.1%	64.7%	66.2%
Mood or emotions	55.9%	49.5%	74.0%
Ability to complete usual daily tasks	46.8%	45.9%	49.4%
Self-esteem/self-imaging	43.4%	41.3%	49.4%
Work or studies	41.7%	39.9%	46.8%
Relationships with family or friends	36.6%	34.9%	41.6%

Notes: [a]Out of all respondents, proportion of patients who reported ever experiencing each side effect while taking an sMRA. [b]Out of those reporting experiencing each side effect, proportion of patients who reported the side effect or symptom ≥1 time per week. [c]Out of those reporting experience ≥1 side effect, proportion of patients who reported being at least "a little" affected.

provider told them to stop taking it or recommended another medication as a reason for discontinuation. Side effects were reported as a reason for discontinuation by 39.0% of past users.

Discussion

This is one of the first real-world evidence studies to collect information on patient perspectives regarding sMRA side effects and discontinuation. This study included 600 respondents, 24.3% of whom had discontinued sMRA treatment within

Table 3 Treatment Discontinuation Among Past Users

	Past Users
Reported reasons for discontinuation, %	
My healthcare provider told me to stop taking it	47.9%
I did not like the side effects associated with it	39.0%
I did not feel that it was working	37.0%
My healthcare provider recommended another medication	31.5%
I was not satisfied with it	30.8%
I did not like the way it made me feel	30.1%
I did not think I needed it	28.8%
I did not like the way it interacted with other medications I took	14.4%
I had trouble remembering it	13.7%
It interfered with my social life	5.5%
The medication was too expensive or not affordable	5.4%
I felt pressured from someone	4.1%
My insurance did not cover it	2.7%

the 12 months prior to the survey date and were identified as past users. This proportion is lower than that observed in other literature or the claims-based RELICS study.[5–9] The discrepancy may be due to this study's selection criteria, which required that patients have used sMRAs within 18 months prior to the survey date. As most respondents were spironolactone users, study findings primarily apply to this population rather than to patients using eplerenone. This predominance reflects US clinical practice, where spironolactone is the overwhelmingly most commonly prescribed sMRA.

The majority of past users were female, younger, and generally had fewer comorbidities than current users. These findings align with the results from the claims-based RELICS study, which suggested that patients with CV-related comorbidities, such as HF, are less likely to discontinue sMRA treatment.[10] However, these results contradict the findings of a study by Jonsson et al, which found that older patients with more comorbidities were more prone to discontinue the treatment.[9] This disparity could be due to the different patient groups considered in the studies. This study and the claims-based RELICS study analyzed discontinuation rates among all sMRA-using patients. On the other hand, Jonsson et al's study specifically focused on HF patients using sMRAs. This group inherently carries a higher CV risk than the broader population of sMRA users.

Respondents' experiences of side effects while on sMRA varied. The instances of side effects also fluctuated in the claims-based RELICS study. However, a noticeable contrast was observed in the higher percentage of male respondents who reported symptoms of gynecomastia compared to the percentage of male patients with gynecomastia recorded in medical claims (17.4% vs 2.9%, respectively).[10] In particular, the proportion of male past users with symptoms of gynecomastia (33.3%) was higher than observed in RELICS. This discrepancy suggests that the impact of male gynecomastia on patients may be more significant than what is typically coded in medical claims. This variation could be because the patient's perception of the situation deviates from the clinical diagnoses or due to underreporting of side effects and their symptoms, including male gynecomastia, in medical claims.

Past users consistently reported experiencing side effects more often, with greater frequency and were more negatively affected. Interestingly, less than half of past users indicated that these side effects were crucial in their decision to discontinue the treatment. This finding highlights a discrepancy between experience with side effects and reasons for discontinuation. These findings are consistent with a related study in a HFrEF patient population that found

MRA discontinuations were often due to renal dysfunction and hyperkalemia and identified predictors of discontinuation such as increased potassium, decreased eGFR, and higher comorbidity index.[9]

Our study found that healthcare providers' recommendations significantly affected respondents' decisions to discontinue use of sMRAs. This corroborates existing research, suggesting that healthcare providers' advice greatly impacts patients' decisions about their health.[13–15] Providers typically base their recommendations on the effectiveness of the medication, the patient's willingness to tolerate symptomatic side effects and the presence of clinical adverse effects such as hyperkalemia.[16] Therefore, decisions to discontinue sMRAs may be more influenced by healthcare providers' recommendations and their understanding of the overall adverse effect burden, rather than the patients' perceptions, highlighting a complex interplay between patients' experiences and clinical guidance.

Study findings should be examined under potential limitations. Participation in the survey was voluntary, possibly leading to selection bias if respondents differed systematically from non-respondents. Additionally, recall bias may impact the accuracy of some responses due to the time lapse between patients' identification and the survey administration, influencing precise recall of events over the past 12 months. Hence, these factors may affect the results.

Conclusion

These findings indicate that the experience of side effects may contribute to decisions regarding sMRA discontinuation, especially as mediated by providers' influence on decision-making. About half of all respondents reported experiencing side effects, which affected patients' quality of life, especially their ability or willingness to engage in vigorous recreational or exercise activities. Past users consistently reported experiencing a higher rate of each side effect more frequently and were more negatively impacted by them. However, the exact factors leading to the discontinuation of sMRAs still require further exploration. Less than half of past users linked any given reason to their decision to discontinue treatment or cited side effects as a contributing factor. This reflects a disparity between patient experience and perception. One clear takeaway from the study is the significant influence healthcare providers have on the decision to initiate or discontinue sMRA treatment. Future research should explore the factors influencing healthcare provider decision-making regarding treatment options, as this can provide more insight into treatment decisions.

Funding

This study was funded by Bayer AG.

Disclosure

ELR, JJS, VJW, and CCT are employees of Carelon Research, which was under contract by Bayer AG to perform this research. NRD received grants from Amgen, AstraZeneca, and CSL Vifor, and honoraria as consultant from Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Cytokinetics, Verve, Merck, Novartis, SC Pharmaceuticals, and CSL Behring. AG and RS were employees of Bayer during the conduct of the study. CS, KF, EP, and NGO are employees of Bayer, which funded the study. The authors report no other conflicts of interest in this work.

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